REMARKS

Claims 1-13 and 23-33 are currently pending in this application. As part of this Amendment and Response, claims 1-3, 5-7, 10-13, and 25-29 have been amended, and claims 23 and 24 have been canceled. Reconsideration of claims 1-13 and 25-33 is respectfully requested.

Objection to the Specification

The Examiner objects to the specification because it lacks a section referring to parent applications and the current status of each. The specification has been amended on page 1 to overcome this objection.

The Examiner asserts that the specification fails to comply with 37 C.F.R. 1.58(a) by virtue of containing drawings on pages 10-15, which should be submitted on separate drawing sheets. The Examiner also suggests renumbering the various Figures on pages 17-24, and adding a section headed "Brief Description of Drawings" to the specification to describe all the drawings without entry of new matter. In addition, the Examiner asserts that Tables 1-3 (and presumably Tables 7-11) on pages 25-29 and 33-36 should be canceled because they contain material presented in the SEQ ID NO: listing and are wasteful of space. Thus, the

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Examiner suggests the deletion of these tables and the renumbering of Tables 4-6 as 1-3.

The specification has been amended to delete the five drawings on pages 10 and 12-15 of the specification; those drawings have been added as new Figures 3-7 in the attached Request for Approval of Drawing Changes submitted concurrently herewith. No new matter has been added.

Table 1 has been canceled, and the specification has been amended on page 4 to present the sequences of canceled Table 1 as SEQ ID NO:1 and SEQ ID NO:2. Tables 2-3 and 7-11 have been canceled; these Tables have been renamed and added as new Figures 2, 8, 13, and 16 in the attached Request for Approval of Drawing Changes submitted concurrently herewith. (Note: New Figure 8 combines canceled Tables 7-9.) No new matter has been added.

Tables 4-6 have been renumbered in the specification as Tables 1-3, as suggested by the Examiner. A section entitled "Brief Description of the Drawings" has also been added to describe the twenty Figures, which now include original Figure 1, new Figures 3-8, 13, and 16 (corresponding to deleted drawings and Tables in the specification), and renumbered Figures 9-12, 14, 15, 17-20 (corresponding to original Figures 2-11). All references in the specification to these Figures and Tables have

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been corrected. Accordingly, applicants request withdrawal of the objection to the specification.

Rejection Under 35 U.S.C. § 101

The Examiner rejected claim 26 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific asserted utility or a well-established utility. (Office Action, page 3.) Specifically, the Examiner contents that activation of prodrugs to active drugs is not a conventional step of immuno-diagnostic aid, and one of skill in the art would not readily envision how to use the recited compound as a diagnostic aid since no direction has been give as to how this compound is to be used. Applicants respectfully traverse.

The recited compound of claim 1 comprises an antigen binding region linked to at least one prodrug-activating enzyme. There are commonly used prodrugs available that offer routine ways to obtain a read-out signal once a prodrug activating enzyme specified in claim 1 has bound to its antigen. For example, the compound X-Gal (5-Chlor-4-Brom-3-indolyl-β-D-galaktosid) is a routinely used molecule in areas such as microbiology or immunology. This compound is cleaved by galactosidases in such a way that a blue colored molecule is released from a colorless

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precursor. One skilled in the art would immediately recognize X-Gal as an example of a tool for creating a read-out signal with a compound of claim 1. Thus, the rejection under 35 U.S.C. § 101 should be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner also rejected claim 26 under 35 U.S.C. § 112, first paragraph. (Office Action, page 3.) The Examiner contents that one skilled in the art would not know how to use the claimed invention since the claimed invention is not supported by either a specific asserted utility or a well-established utility. Applicants traverse.

As discussed above, the claimed invention is supported by a well-established utility because one skilled in the art would immediately recognize well known compounds, such as X-Gal, as tools for creating a read-out signal with a compound of claim 1. Thus, the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-13 and 23-33 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing

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to point out and distinctly claim the subject matter which applicants regard as the invention. (Office Action, pages 3-4.)

Specifically, the Examiner asserts that claim 1 is indefinite by reciting "antigen binding region" and then reciting "which is bound," since it implies that the antigen binding region binds the enzyme. Applicants have amended claim 1 to substitute "linked" in lieu of "which is bound." Applicants believe that this claims is now definite.

The Examiner also contends that claims 3 and 30 are inconsistent with base claim 1 and are unclear because they are directed to a compound containing sFv, which would be monovalent, not bivalent or multivalent. Applicants submit that claims 1, 3 and 30 are directed to compounds comprising an antigen binding region with a bivalent or multivalent structure. As recited in claim 3, "the antigen binding region comprises a variable domain of a heavy antibody chain and a variable domain of a light antibody chain (sFv fragment)." In other words, the antigen binding region of claim 3 comprises an sFv fragment; the sFV fragment is part of the bivalent structure or multivalent structure. (*See also* specification, page 2, lines 21-28.)

Likewise, the "sFv-β-lactamase fusion protein" of claim 30 also comprises a bivalent or multivalent structure. For example,

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as discussed on page 5 of the specification, "the functional enzymatically active sFv-β-lactamase fusion protein is in the form of a 'bivalent molecule'." (Specification, page 5, lines 31-33.) Thus, applicants submit that claim 3 and 30 are definite.

The Examiner further asserts that claims 5 and 6 recite an improper Markush group, and that "the TAA" of claim 5 lacks an antecedent basis in claim 3. Claims 5 and 6 have been amended to overcome these rejections. The Examiner also asserts that claim 7 is unclear by reciting "β-glucuronidase", that claims 3 and 13 are unclear by reciting "undergoes", and that claim 27 is unclear by misspelling "Bacillus". Claims 3, 7, and 13 have been amended according to the Examiner's suggestions.

Claims 23 and 24 have been rejected under 35 U.S.C. § 101 because of the claimed recitation of a use, without setting forth any steps involved in the process. (Office Action, page 5.) Applicants have canceled claims 23 and 24, thus rendering any rejections of these claims moot.

Applicants believe that these claims are now in condition for allowance. Accordingly, applicants request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

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Rejections Under 35 U.S.C. § 103(a)

Claims 1-9, 23-27, 30 and 33 were rejected by the Examiner under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bosslet et al. (Brit. J. Cancer) or Seemann et al. (English equivalent, CA 2,062,047) in view of Huston et al. (U.S. Pat. No. 5,132,405) and as necessary Bosslet et al. (English equivalent, U.S. Pat No. 5,591,828) and Eaton et al. (Office Action, pages 5-8.)

The Examiner asserts that the primary references, Bosslet et al. (Brit. J. Cancer) and Seemann et al., disclose a fusion protein comprising a Fab (derived from a humanized version of anti-CEA antibody 431), a linker, and a human β-glucuronidase. According to the Examiner, this protein differs from the claimed invention by virtue of having an Fab (composed of H and L chains) instead of having an antigen binding region compound of a single polypeptide formed from V_H and V_L segments. The Examiner then contends that Huston et al. teaches that an antigen binding region may be present in multiple copies and that the antigen binding region(s) may be fused to other functional molecules, such as enzymes. The Examiner then argues that it would have been obvious to modify the fusion protein constructs of the primary reference by substituting the single chain antigen

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binding polypeptides of Huston et al. for the Fab of the construct. Applicants traverse.

Applicants' invention is directed to a compound comprising an antigen binding region composed of a single polypeptide chain that is linked to at least one prodrug-activating enzyme, where the antigen binding region has a bivalent or multivalent structure. In contrast, Bosslet et al. and Seemann et al. describe two DNA constructs, one containing a V_H gene, a C_H1 exon, a hinge exon, and a cDNA coding for β-glucuronidase, and the other containing a V_L gene, a C_K gene, and a signal exon. (*See e.g.*, Bosslet et al., page 235, left column and chart 1 and 2.) These references suggest the transfection of cells with these plasmids (along with two other plasmids carrying drug resistance genes), which in turn may lead to the expression and association of the V_H and V_L polypeptides to form an Fab fragment. Neither reference, however, teaches or suggests the transfection of a cell with a plasmid carrying an entire Fab or sFv (composed of both H and L chains) linked to β-glucuronidase. Likewise, these references never discuss or suggest an antigen binding region composed of a single polypeptide chain, whether that antigen binding region be linked to a prodrug-activating enzyme or have a bivalent or multivalent structure.

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The single chain Fv of Huston et al. consists of a single polypeptide chain with a sequence coding for V_H-linker-V_L or V_L-linker-V_H,[1] as compared to the classical Fv heterodimer of V_H and V_L. Applicants point out that two distinct protein domains do not refold into the same structure when composed of two single peptide chains as compared to one single polypeptide chain construct connecting the domains by means of a linker or spacer. For example, the linker itself would be expected to form a structure of its own, thereby disturbing the overall shape of the molecule. (*See e.g.*, Huston et al. (Methods), page 55, first full paragraph.) Moreover, the situation is even more complex when three different domains have to be taken into account.

Thus, it would not have been obvious to one skilled in the art to replace the V_H or V_L genes of Bosslet et al. or Seemann et al. with the DNA sequence coding for the single polypeptide chain Fv of Huston et al., which codes for two distinct protein domains in a single molecule. Moreover, one skilled in the art would have expected a linkage to a third domain, *e.g.*, a prodrug-activating enzyme, to cause serious interference between the

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[1] Likewise, the receptor of the '828 patent (Bosslet et al.) produced by gene manipulation consists of a sequence coding for a V_H/C_H1-spacer-V_H/C_H1. This fragment, however, is not an sFv fragment or a single chain antigen binding region since it contains two V_H domains, rather than a V_H and V_L domain.

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different molecule domains, thereby resulting with a high probability in inactive molecules. Likewise, the Fab fusion protein of Bosslet et al. (created upon transfection of multiple plasmids) and the single chain Fv polypeptide of Huston et al. would not have been recognized as functional equivalents, because it would have been impossible to predict functionality of Fab compared to sFv with respect to a linked enzyme.

The Examiner contends that one would have been motivated to use the sFv of Huston et al. in lieu of Fab since the former can have increased stability, and can penetrate tissues more rapidly than antibodies or their conventionally produced fragments. Applicants submit that while it is possible that an antigen binding site would have increased stability, it is not obvious that a sFv construct would be more stable.

In contrast, one of skilled in the art would expect that sFv constructs in many cases, depending on their variable sequences, would fold into structures with lower affinities compared to their Fab equivalents. Moreover, the interaction with a third domain, such as an enzyme, even further complicates predictions on stability and affinity. Thus, when comparing either stability or affinity/avidity, one skilled in the art would not have been motivated to use the sFv of Huston et al. instead of Fab in a

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construct. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is requested.

With regard to claims 23-26 and 33 (directed to pharmaceutical or diagnostic compositions, their use thereof, and a method of treatment), the Examiner asserts that Bosslet et al. and Seemann et al. teach a potential therapeutic use, and that compositions disclosed in those references would include those where the binding and enzymatic activity of the polypeptide would be evaluated. As discussed above, claims 23 and 24 have been canceled, and the basic molecules disclosed by the above-mentioned references for therapeutic or diagnostic use are different from the molecular construct of applicants' invention as claimed in claims 25, 26 and 33. Thus, the rejection under 35 U.S.C. § 103(a) should be withdrawn.

With regard to claims 27 and 30, the Examiner asserts that beta-lactamase is taught by Eaton et al. as a prodrug-activation enzyme, including one obtained from *B. Cereus*. As discussed above, when comparing either stability or affinity/avidity, one skilled in the art would not have been motivated to use the sFv from Huston et al. in place of Fab of Bosslet et al. or Seemann et al. (as created by the expression of the two V_H gene and V_L gene constructs), particularly in the situation where the

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fragment is linked to a prodrug-activation enzyme. Moreover, the significance of Eaton et al., as is clear from the claims of this reference, is the disclosure of certain prodrugs having a β-lactamase action that can be used in immunoconjugates. Eaton et al. does not disclose a compound comprising an antigen binding region that is composed of a single polypeptide chain, where the antigen binding region has a bivalent or multivalent structure. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is requested.

Claims 1, 11, 12, 31, and 32 were also rejected by the Examiner under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bosslet et al. (Brit. J. Cancer) or Seemann et al. in view of Huston et al. (the '405 patent) and as necessary Bosslet et al. (the '828 patent) and Eaton et al., and in further view of Ong et al., Bagshawe et al., and Huston et al. (Methods Enzymol.). (Office Action, pages 8-10.)

In particular, the Examiner contents that Huston et al. (Methods) teaches that polypeptides containing sFv may be secreted into the periplasmic space of Gram-negative bacteria and be properly refolded with the correct disulfide bonds, and that one of ordinary skill in the art would have recognized that polypeptides produced by *E. coli* would not be glycosylated. The

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Examiner also asserts that Ong et al. teaches that it is advantageous to permit rapid clearing of circulating therapeutic antibodies in a treated individual by providing galactosyl moieties on the antibodies, and that such clearing would be advantageous wherein antibody-enzyme conjugates that convert a prodrug to an active drug are employed. As with Ong et al., the Examiner also alleges that Bagshawe et al. teaches the desirability of placing galactosyl and/or mannosyl moieties on an antibody that is a member of an antibody-prodrug activating enzyme conjugate.

The rejection by the Examiner is based upon the argument that Ong et al. and Bagshawe et al. teach that providing galactosyl moieties on antibodies (which are members of an antibody-prodrug activating enzyme conjugate) is advantageous, and since antibody enzyme conjugates and sFv-enzyme fusion proteins are functionally equivalent, it would have been obvious to provide galactosyl moieties on sFv-enzyme fusion proteins, so that these could be rapidly cleared from circulation. Applicants traverse.

Specifically, applicants point out that antibodies (and their fragments, such as F(ab)'2) differ from sFv fragments in a number of important ways. For example, they differ in size,

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domain arrangement, inter- and intramolecular interactions, as well as accessibility to molecular parts that are to be glycosylated. Glycosylation, therefore, would have been expected to result in different structural compositions for both molecule species with serious impact on stability, clearance rate or affinity. Thus, the rejection under 35 U.S.C. § 103(a) is not supported by the details of these references and should be withdrawn.

Claims 10, 13, and 29 were also rejected by the Examiner under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bosslet et al. (Brit. J. Cancer) or Seemann et al. in view of Huston et al. (the '405 patent) and as necessary Bosslet et al. (the '828 patent) and Eaton et al., and in further view of Ong et al., Bagshawe et al., and Huston et al. (Methods Enzymol.), and in further view of Goochee et al. (Office Action, pages 10-11.)

The Examiner contents that Goochee et al. shows that it was known that yeast could be used to express polypeptide having a high degree of mannosylation and having a rapid clearance rate. Thus, the Examiner asserts it would have been obvious to express the polypeptide of claim 1 in yeast in order to provide polypeptides having mannose moieties that would allow for effective clearance of the polypeptide.

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As previously discussed, none of the cited references teach or suggest an antigen binding region composed of a single polypeptide chain that is linked to at least one prodrug-activating enzyme, where the antigen binding region has a bivalent or multivalent structure. Furthermore, as with the antibodies of Ong et al. and Bagshawe et al., the proteins/polypeptides discussed in Goochee et al. are not functionally equivalent to the single chain antigen binding peptide of applicants' invention. Different polypeptides will differ in size and inter- and intramolecular interactions, as well as accessibility to molecular parts that are to be glycosylated. Thus, glycosylation would have been expected to result in different structural compositions for different polypeptides with serious impact on stability, clearance rate or binding affinity.

The Examiner further asserts that the species recited in claim 13 is specifically taught by Goochee et al. at page 1348. Even assuming a particular oligosaccharide is disclosed in Goochee et al. or any other reference, however, none of the cited references teach or suggest an antigen binding region composed of a single polypeptide chain that is linked to at least one prodrug-activating enzyme, where the antigen binding region has a

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bivalent or multivalent structure. The fact that any protein or polypeptide can be glycosylated via secretory expression in *S. cerevisiae* does not render applicants compounds (glycosylated or otherwise) obvious to one skilled in the art.

Likewise, even assuming the carboxypeptidase G2 from *Pseudomonas* has been shown to be a prodrug enzyme in antibody enzyme conjugates, none of the cited references disclose applicants' compound. Antibodies, proteins, and polypeptides generally are not functionally equivalent to an antigen binding region composed of a single polypeptide chain that has a bivalent or multivalent structure.

For the reasons set forth above, applicants respectfully submit that the teachings of Bosslet et al. (Brit. J. Cancer), Seemann et al., Huston et al. (the '405 patent), Bosslet et al. (the '828 patent), Eaton et al., Ong et al., Bagshawe et al., Huston et al. (Methods Enzymol.), and Goochee et al., either alone or in combination, do not render the claimed invention obvious. Nothing in these references suggests the combination of these references to elucidate a compound comprising an antigen binding region composed of a single polypeptide chain that is linked to at least one prodrug-activating enzyme, where the antigen binding region also has a bivalent or multivalent

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structure. Accordingly, applicants request withdrawal of the rejections under 35 U.S.C. § 103. Applicants respectfully request reconsideration of this application and allowance of the pending claims.

Double Patenting Rejection

Claims 1-10, 12, 13, 25, 26, 30 and 33 were provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-10, 12, 13, 25, 26, 28 and 29 of co-pending application Serial No. 09/178,564. (Office Action, page 11.) In addition, claims 11, 23, 24, 27-29, and 31-32 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 10, 11, and 30 of co-pending application Serial No. 09/178,564. (Office Action, page 12.) As these are provisional double patenting rejections, the Examiner is respectfully requested to hold the rejections in abeyance pending an indication of allowable subject matter in this application or the related application.

In view of the foregoing amendments and remarks, applicants respectfully request the reconsideration of this application and

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the timely allowance of the pending claims. Applicants believe that the claims are now in condition for allowance.

Applicants believe that any extension of time required under § 1.136(a) to file this Amendment and Response is accounted for by the Petition for Extension of Time filed concurrently herewith. However, if a further extension is required, such extension is hereby requested and any additional fees due in connection with the filing of this Amendment and Response should be charged to Deposit Account No. 06-0916.

Respectfully submitted,

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